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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,651	07/12/2001	Hiroyuki Nakane	77670/495	2816

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/902,651	NAKANE ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7,11-16 and 49-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,11-16 and 49-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/898,560.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/07 has been entered.

[2] Claims 1-4, 6-7, 11-16, and 49-53 are pending in the application.

[3] Applicant's amendment to the claims, filed on 10/30/07, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's arguments filed on 10/30/07 in response to the Office action mailed on 8/6/07 are acknowledged. Applicant's arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Reissue Oath/Declaration

[6] Applicant is reminded of MPEP 1444.II, which states (in relevant part), "[a] supplemental oath/declaration need not be submitted with each amendment and additional correction. Rather, it is suggested that the reissue applicant wait until the case is in condition for allowance, and then submit a cumulative supplemental reissue oath/declaration pursuant to 37 CFR 1.175(b)(1). See MPEP § 1414.01 for a discussion of the required content of a supplemental reissue oath/declaration under 37 CFR 1.175(b)(1).

[7] The reissue oath/declaration filed with this application is defective (see 37 CFR 1.175 and MPEP § 1414) because of the following: the reissue Declaration states, "duty to disclose under 37 CFR 1.56(a)." However, the duty to disclose should be made under all sections of 37 CFR 1.56, not just 37 CFR 1.56(a). Appropriate correction is required.

RESPONSE TO ARGUMENT: At the middle of p. 8 of the instant remarks, applicant acknowledges the instant objections to the reissue oath/declaration and responds by stating that "the defective reissue oath/declaration will be corrected by submitting a substitute reissue oath/declaration when...the Examiner indicates that the reissue application is in a condition for allowance".

As the defective reissue declaration has not been corrected, the objections to the reissue Declaration as set forth in the prior Office action and reiterated above are maintained for the reasons of record.

Claim Objection

[8] Claims 11 and 16 are objected to in the recitation of "an enzyme" in referring to a "mutant prenyl diphosphate synthase". While a skilled artisan would consider "A mutant prenyl diphosphate synthase" to be "an enzyme", in order to improve claim form, it is suggested that, for example, the phrase "an enzyme" in claims 11 and 16 be replaced with "the mutant prenyl diphosphate synthase".

[9] Claim 15 is objected to in the recitation of "coding for" in line 3 and in order to improve claim form, it is suggested that, for example, the term "coding for" be replaced with the art-recognized term "encoding". See, *e.g.,* claim 11, which recites "A DNA encoding..."

[10] Claims 49-53 are objected to as omitting a claim status identifier, *e.g.,* "(New)". Appropriate correction is required.

Claim Rejections – Defective Oath/Declaration

[11] Claims 1-4, 6-7, 11-16, and 49-53 are rejected as being based on a defective Oath/Declaration for the reasons set forth above.

RESPONSE TO ARGUMENT: At the top of p. 9 of the instant remarks, applicant acknowledges the defective reissue oath/declaration and responds by stating that "the defective reissue oath/declaration will be replaced with a substitute reissue oath/declaration when the Examiner indicates that the application is in a condition for allowance".

As the defective reissue declaration has not been corrected, the objections to the reissue Declaration as set forth in the prior Office action and reiterated above are maintained for the reasons of record.

Claim Rejections - 35 USC § 112, Second Paragraph

[12] Claims 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is noted that a rejection based on the reasoning set forth below has yet to be presented. However, upon further consideration, the claims are rejected for reasons that follow.

Claim 15 (claim 16 dependent therefrom) recites the limitation "the expression product". Although it is acknowledged the host cell is transformed with "an expression vector," there is no requirement that an "expression product" be produced from the expression vector and a skilled artisan would recognize that the host cell would produce numerous other "expression products". As such, there is insufficient antecedent basis for the limitation of "the expression product" in the claim.

Also, it is noted that claim 15 is drawn to a "process for producing a mutant prenyl diphosphate synthase..." Although the method recites the two active steps of "culturing a host..." and "harvesting the expression product", it is noted that neither step requires production of the mutant prenyl diphosphate synthase and "the expression product" of the harvesting step is not required to be the recited "mutant prenyl diphosphate synthase". As such, the method would appear to be incomplete since the

recited active method steps do not appear to achieve the desired production of a "mutant prenyl diphosphate synthase according to claim 1".

Claim Rejections - 35 USC § 112, First Paragraph

[13] The written description and scope of enablement rejections of claims 1-4, 6-7, 11-16, and 49-53 under 35 U.S.C. 112, first paragraph, as set forth at paragraphs 12 and 13 of the 8/6/07 Office action are withdrawn in view of applicant's amendment to limit the mutations of claim 1 to SEQ ID NO:1, except the mutations of: 1) T78F and H81A; 2) T78F and H81L; 3) F77Y, T78F, and H81L; 4) F77Y, T78F, and H81A; or 5) F77Y, T78S, V80I, I84L, and 84PS85.

[14] The new matter rejections of claims 2, 7, and 16 under 35 U.S.C. 112, first paragraph, are maintained for the reasons of record and the reasons stated below. The rejections were fully explained in prior Office actions. See paragraphs 14 and 15 of the 8/6/07 Office action.

RESPONSE TO ARGUMENT: At page 10 of the instant remarks, applicant argues the rejections are obviated by amendment to replace the phrase "under similar conditions" with "under identical conditions". According to applicant, the Office Action concedes this limitation has descriptive support in the specification.

Applicant's argument is not found persuasive. It appears applicant has mischaracterized the examiner's position in the prior Office action. As noted in the prior Office action, "Figure 3 may provide inherent support for the limitation of synthesizing

more farnesyl diphosphate than the amount of farnesyl diphosphate synthesized by the wild type prenyl diphosphate synthase under identical conditions *as set forth at Example 5 (columns 12-14)* for those specific mutants as disclosed in Figure 3 of the specification" (emphasis added; see paragraph 14 of the 8/6/07 Office action) and "Figure 2 and the disclosure at column 13, lines 1-14 may provide inherent support for the limitation of the mutants of Figure 2 having a higher relative activity using isopentenyl diphosphate as a substrate at a temperature of 80 °C and under identical conditions *as set forth at Example 5 of the specification* than that of the wild-type prenyl diphosphate synthase" (emphasis added; see paragraph 15 of the 8/6/07 Office action). In this case, applicant is relying on the results shown in Figure 2 or 3 as providing inherent support for a claim limitation. The results shown in Figure 2 or 3 are based on a specific set of experimental conditions and applicant is relying on the results of Figure 2 or 3 as inherent support for the claim limitations. Thus, while the specification would appear to provide descriptive support for the recited comparison under the identical conditions under which the Figure 2 or 3 experiments were conducted (as set forth in Example 5 of the specification), it would appear that the specification fails to provide descriptive support for the recited comparison between the mutant and wild-type under *any* identical conditions, namely those conditions outside of those conditions disclosed in Example 5 of the specification.

[15] Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection. It is noted that a rejection based on the reasoning set forth below has yet to be presented. However, upon further consideration of the claims, particularly a broad, but reasonable interpretation of claims 12 and 13, the claims are rejected for reasons that follow.

According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

Claim 12 is drawn to a genus of RNAs transcribed from "a DNA according to claim 11". Claim 13 (claim 14 dependent therefrom) is drawn to a genus of recombinant vectors comprising "a DNA according to claim 11". In view of the recitation of the indefinite article "a" in the phrase "a DNA according to claim 11", the phrase "a DNA according to claim 11" has been interpreted as encompassing fragments and subsequences of "A DNA encoding an enzyme according to claim 1". As such, claims 12 and 13 have been interpreted as encompassing a genus of RNAs transcribed from fragments of "A DNA encoding an enzyme according to claim 1" or a genus of recombinant vectors comprising as few as two contiguous dexoynucleotides of "A DNA encoding an enzyme according to claim 1".

The Federal Circuit in *UC California v. Eli Lilly* (43 USPQ2d 1398) has said that a sufficient written description of a genus of DNAs may be achieved by a recitation of a representative number of DNAs defined by nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In this case, the specification discloses five representative species of the claimed genus of RNAs or recombinant vectors, *i.e.,* an RNA encoding Mutant enzyme 1: SEQ ID NO:1, except Thr78 is replaced with Phe and His81 is replaced with Ala; Mutant enzyme 2: SEQ ID NO:1, except Thr78 is replaced with Phe and His81 is replaced with Leu; Mutant enzyme 3: SEQ ID NO:1, except Phe77 is replaced with Tyr, Thr78 is replaced with Phe, and His81 is replaced with Leu; Mutant enzyme 4: SEQ ID NO:1, except Phe77 is replaced with Tyr, Thr78 is replaced with Phe, and His81 is replaced

with Ala; Mutant enzyme 5: SEQ ID NO:1, except Phe77 is replaced with Tyr, Thr78 is replaced with Ser, Val80 is replaced with Ile, Ile84 is replaced with Leu, and an insertion of Pro-Ser between Ile84 and Met85 OR a recombinant vector encoding Mutant enzyme 1, 2, 3, 4, or 5. Other than these five representative species of each respective genus, the specification fails to describe any additional representative species of the claimed genus of RNAs or recombinant vectors.

In this case, the genus encompasses all species of RNAs transcribed from or recombinant vectors comprising fragments of "A DNA encoding an enzyme according to claim 1". The genus of transcribed RNAs is not limited to those that translate the Mutant enzyme 1, 2, 3, 4, or 5, and instead encompasses RNA fragments and variants. Also, it is noted that the genus of recombinant vectors comprises DNAs that encode polypeptides having any function, including polypeptides that are non-functional and polypeptides that have an activity that is distinct to that of prenyl diphosphate synthase. Thus, it is the examiner's position that the five disclosed representative species of each respective genus fail to reflect the variation among the members of the genus, which encompass widely variant species with respect to both structure and function.

Given the lack of description of a representative number of polypeptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[16] Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an RNA encoding Mutant enzyme 1, 2, 3, 4, or 5 (as set forth above) or a recombinant vector comprising DNA encoding Mutant enzyme 1, 2, 3, 4, or 5, does not reasonably provide enablement for *all* RNAs and recombinant vectors as broadly encompassed by the claims. It is noted that a rejection based on the reasoning set forth below has yet to be presented. However, upon further consideration of the claims, particularly a broad, but reasonable interpretation of claims 12 and 13, the claims are rejected for reasons that follow.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims...and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP

2164.08 states, "[a]ll questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims" (citation omitted) and "[w]hen analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification."

As noted above, claim 12 is drawn to an RNA transcribed from "a DNA according to claim 11". Also as noted above, claim 13 (claim 14 dependent therefrom) is drawn to a recombinant vector comprising "a DNA according to claim 11". In view of the recitation of the indefinite article "a" in the phrase "a DNA according to claim 11", the phrase "a DNA according to claim 11" has been interpreted as encompassing fragments of "A DNA encoding an enzyme according to claim 1". As such, claim 12 has been interpreted as being transcribed from fragments of "A DNA encoding an enzyme according to claim 1" and claim 13 has been interpreted as encompassing any recombinant vector comprising as few as two contiguous dexoynucleotides of "A DNA encoding an enzyme according to claim 1". Also, regarding the scope of transcribed RNAs, it is noted that since the process of transcribing DNA to RNA requires transcription initiation and termination sequences, a DNA encoding only the polypeptide of claim 1 would not appear to result in transcription of an RNA.

The enablement provided by the disclosure of the specification is not commensurate with the scope of the claims, particularly with respect to the DNAs of the

recombinant vector. In this case, the specification fully enables an RNA or a recombinant vector encoding Mutant enzyme 1, 2, 3, 4, or 5 as set forth above.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: Regarding the scope of recombinant vectors, it is noted that the polypeptide's encoding nucleotide sequence determines the polypeptide's structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.,* expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high level of unpredictability associated with altering the amino acid sequence of a polypeptide.

The state of the art provides evidence for the high degree of unpredictability in altering a polypeptide's encoding DNA sequence with an expectation that the altered polypeptide will have the desired activity/utility. See the cited teachings of Branden et

al., Witkowski et al., Ohnuma et al., and MPEP 2144.08.II.A.4.(c) as noted in the prior Office action, the teachings of which are undisputed by applicant.

The amount of direction provided by the inventor and The existence of working examples: The specification discloses only five working examples encompassed by the scope of the claimed RNAs and recombinant vectors, *i.e.,* an RNA or a recombinant vector encoding Mutant enzyme 1, 2, 3, 4, or 5 as set forth above.

Regarding the scope of claimed RNAs, it is noted that the specification fails to provide guidance for using all RNA fragments transcribed from "A DNA encoding an enzyme according to claim 1".

Regarding the scope of claimed recombinant vectors, while methods for altering a polypeptide's encoding DNA sequence were known in the art at the time of the invention, the teachings provided by the specification and prior art fail to provide the necessary guidance for making and using the entire scope of claimed recombinant vectors. For example, the specification fails to provide further guidance for altering the DNA encoding the recited mutants by substitution, insertion, addition and/or deletion with an expectation of maintaining the desired biological activity. Moreover, the specification fails to provide any guidance for using those recombinant vectors encoding polypeptides as encompassed by the claims that do not maintain farnesyl diphosphate synthase enzymatic activity.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of transcribing RNA from DNA were known at the time of the invention, it was not routine to make and test all RNAs as

encompassed by the claims, particularly as the specification fails to provide guidance for using those small fragments of RNA as encompassed by the claims that do not translate the protein of claim 1. Also, while methods of generating variants of a DNA encoding a polypeptide are known in the art, *e.g.,* mutagenesis, it is not routine in the art to screen for *all* recombinant vectors encoding polypeptides having a substantial number of substitutions or modifications as encompassed by the instant claims for those that have the ability to synthesize prenyl diphosphate.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation that is required, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

[17] Status of the claims:

- Claims 1-4, 6-7, 11-16, and 49-53 are pending.
- Claims 1-4, 6-7, 11-16, and 49-53 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Steadman/
David J. Steadman, Ph.D.
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Art Unit 1656